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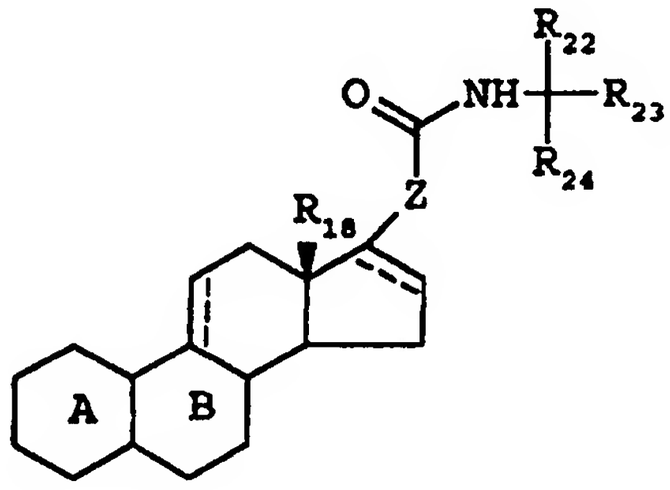
(54) Title: PROCESS FOR PREPARING STEROIDS HAVING A CARBOXAMIDE SIDE-CHAIN

(57) Abstract

Process for preparing steroids having a carboxamide side-chain of formula (I) wherein: the formula - -- are each independently, single or double bonds; z is a single bond, or a straight or branched $C_1$-$C_5$ alkylene; the moiety represents the A and B rings of a steroid; $R_{18}$ is hydrogen or $C_1$-$C_4$ alkyl; $R_{22}$, $R_{23}$, and $R_{24}$ are, each independently, selected from: hydrogen, optionally substituted $C_1$-$C_{10}$ alkyl, $C_5$-$C_7$ cycloalkyl, $C_6$-$C_{10}$ alkylcycloalkyl or cycloalkylakyl, $C_6$-$C_{10}$ aryl, $C_7$-$C_{14}$ arylalkyl or alkylarly, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl. The process comprises reacting the corresponding 17-cyanosteroids with an alcohol, and alkene or a halide. The compounds of formula (I) are useful as testosterone 5α-reductase inhibitors.




(I)

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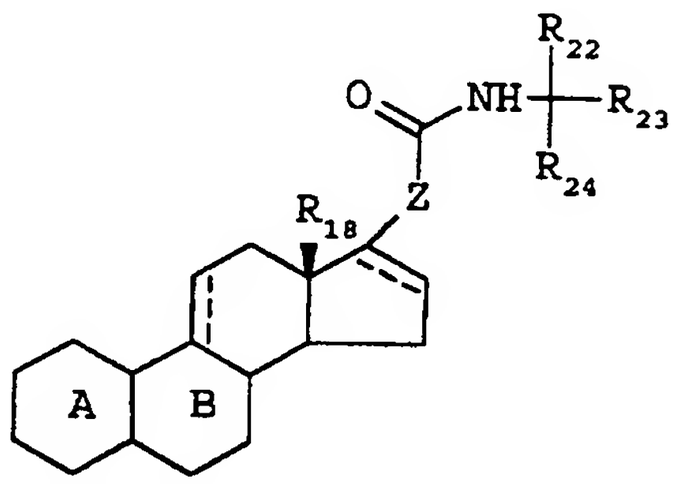
# PROCESS FOR PREPARING STEROIDS HAVING A CARBOXAMIDE SIDE-CHAIN.

The present invention relates to a process for preparing steroids having a carboxamide side-chain. More particularly, the present invention relates to a process for preparing steroids of the general formula:

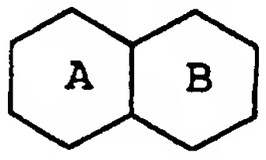


(I)

wherein:

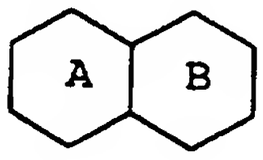
the symbols --- are, each independently, single or double bonds;

Z is a single bond, or a straight or branched $C_1$-$C_5$ alkylene;

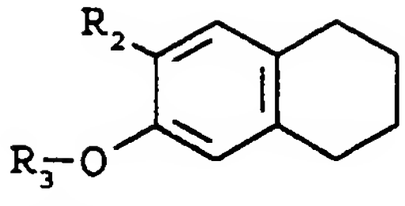
the moiety  represents the A and B rings of a steroid;

$R_{18}$ is hydrogen or $C_1$-$C_4$ alkyl;

$R_{22}$, $R_{23}$, and $R_{24}$ are, each independently, selected from: hydrogen; $C_1$-$C_{10}$ alkyl, optionally substituted by one or more halogen atoms; $C_5$-$C_7$ cycloalkyl; $C_6$-$C_{10}$ alkylcycloalkyl or cycloalkylalkyl; $C_6$-$C_{10}$ aryl; $C_7$-$C_{14}$ arylalkyl or alkylaryl; heterocyclyl; heteroaryl; heterocyclylalkyl; and heteroarylalkyl.

Particularly, the moiety  may be selected from:

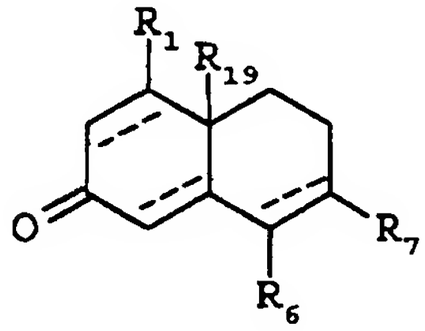
1)



(VI)

wherein: $R_3$ is hydrogen or $C_1$-$C_4$ alkyl; and $R_2$ is hydrogen or $-OR_2'$, wherein $R_2'$ is hydrogen or $C_1$-$C_4$ alkyl;

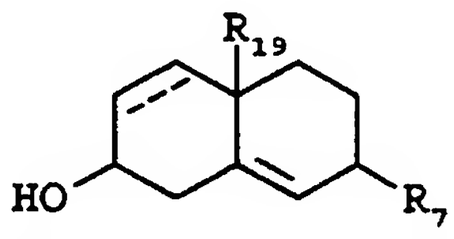
2)



(VII)

wherein: the symbols --- are, each independently, single or double bonds; $R_1$, $R_6$, $R_7$, and $R_{19}$ are, each independently, hydrogen or $C_1$-$C_4$ alkyl;

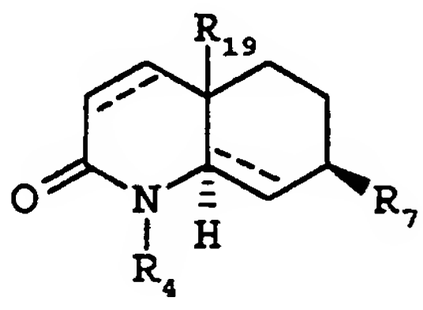
3)



(VIII)

wherein: the symbol --- is a single or a double bond; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl; and $R_{19}$ is hydrogen or $C_1$-$C_4$ alkyl;

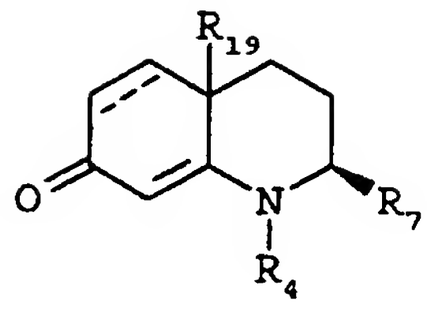
4)



(IX)

wherein: the symbols --- are, each independently, single or double bonds; $R_4$ is hydrogen, $C_1$-$C_4$ alkyl, $C_6$-$C_{10}$ aryl, $C_7$-$C_{10}$ arylalkyl, acetyl, benzoyl, or tosyl; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl; $R_{19}$ is hydrogen or $C_1$-$C_4$ alkyl;

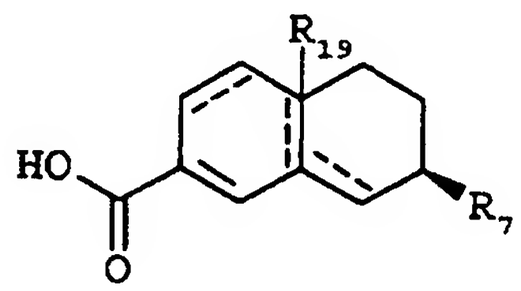
5)



(X)

wherein: the symbol --- is a single or a double bond; $R_4$ is hydrogen, $C_1$-$C_4$ alkyl, $C_6$-$C_{10}$ aryl, $C_7$-$C_{10}$ arylalkyl, acetyl, benzoyl, or tosyl; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl; $R_{19}$ is hydrogen or $C_1$-$C_4$ alkyl;

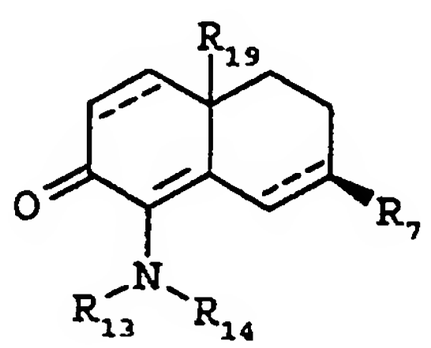
6)



(XI)

wherein: the symbols --- are, each independently, single or double bonds; $R_{19}$ is hydrogen, $C_1$-$C_4$ alkyl, or it is absent when linked to a double-bonded carbon atom; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl;

7)



(XII)

wherein: the symbols --- are, each independently, single or double bonds; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl; $C_{19}$ is hydrogen or $C_1$-$C_4$ alkyl; $R_{13}$ and $R_{14}$ are, each independently, hydrogen, $C_1$-$C_4$ alkyl, $C_6$-$C_{10}$ aryl, $C_7$-$C_{10}$ arylalkyl, acetyl, benzoyl, tosyl or, taken together, phthalyl.

The steroid compounds of formula (I) are known as

pharmacologically active products. For example, the compounds of formula (I) wherein the AB ring moiety has formula (VII) are reported to be testosterone 5α-reductase inhibitors (see, e.g., U.S. Patents No. 4,191,759, 4,220,775, and 4,377,584). The compounds of formula (I) wherein the AB ring moiety has formula (IX) are reported to be testosterone 5α-reductase inhibitors (see, e.g., EP-4949, EP-155046, WO 94/20104, EP-484094, EP-200859, WO 94/03475, WO 95/07927, EP-277002; J. Med. Chem. 27, 1690-1701 (1984) and 29, 2298-2315 (1986)). The compounds of formula (I) wherein the AB ring moiety has formula (X) are reported to be testosterone 5α-reductase inhibitors (see, for example, WO 93/13124; J. Med. Chem. 37, 2352-2360 (1994)). The compounds of formula (I) wherein the AB ring moiety has formula (XI) are reported to be testosterone 5α-reductase inhibitors (see, for example, EP-289327, EP-567271; J. Med. Chem. 33, 937-942 and 943-950 (1990)). The compounds of formula (I) wherein the AB ring moiety has formula (XII) are reported to be testosterone 5α-reductase inhibitors (see, for example, EP-469548, EP-469549).

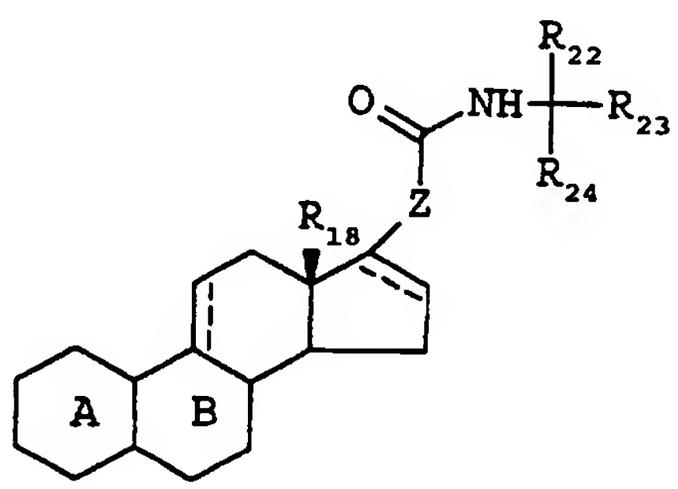
The compounds of formula (I) are usually prepared by condensation reaction of the corresponding 17-carboxylic acid or derivative thereof, such as for example a chloride, a pyridyl thioester, an imidazole or a hydroxybenzotriazole derivative, with a suitable amine.

Such process shows some drawbacks, especially when the amine that has to be condensed with the carboxylic acid is scarcely reactive, because of its sterical hindrance or its poor nucleophilicity, or it is not readily available by synthesis. For example, in the case of the reaction between 3-oxo-4-aza-

5α-androst-1-ene-17β-carboxylic acid and 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propyl amine the corresponding amide is obtained with a yield of about 20% at most. On the contrary, the reaction between 17-cyano-4-aza-5α-androst-1-en-3-one and 1,1,1,3,3,3,-hexafluoro-2-phenyl-2-propyl triflate according to the present invention provides the amide with a yield of about 40%.

The Applicant has now found that the steroids of formula (I) having a carboxamide side-chain can be advantageously prepared by reacting the corresponding 17-cyanosteroids with a suitable alcohol or one of its activated derivative as defined hereinunder.

Therefore, the present invention provides a process for preparing a compound of formula:

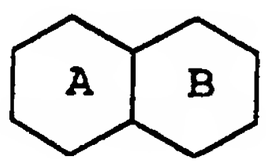


(I)

wherein:

the symbols --- are, each independently, single or double bonds;

Z is a single bond, or a straight or branched $C_1$-$C_5$ alkylene;

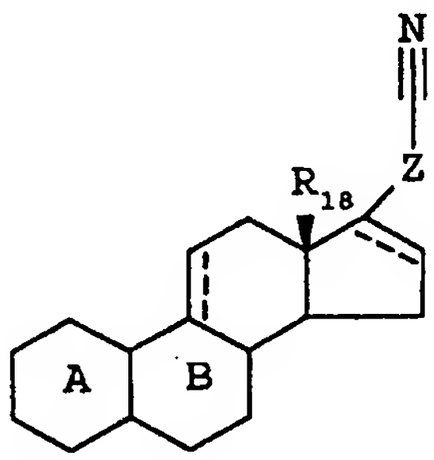
the moiety  represents the A and B rings of a steroid;

$R_{18}$ is hydrogen or $C_1$-$C_4$ alkyl;

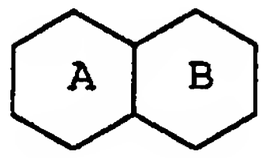
$R_{22}$, $R_{23}$, and $R_{24}$ are, each independently, selected from:

hydrogen; optionally substituted $C_1$-$C_{10}$ alkyl, $C_5$-$C_7$ cycloalkyl, $C_6$-$C_{10}$ alkylcycloalkyl or cycloalkylalkyl, $C_6$-$C_{10}$ aryl, $C_7$-$C_{14}$ arylalkyl or alkylaryl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl;

said process comprising reacting a compound of formula:

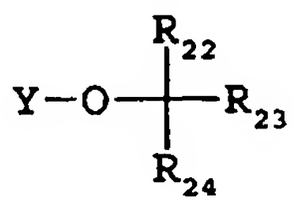



(II)

wherein the symbols ---, Z, $R_{18}$, and the moiety 

are defined as above;

with a compound of formula:

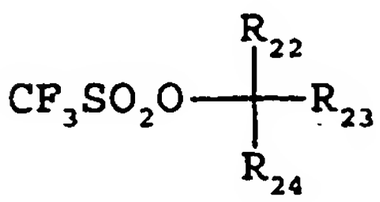



(III)

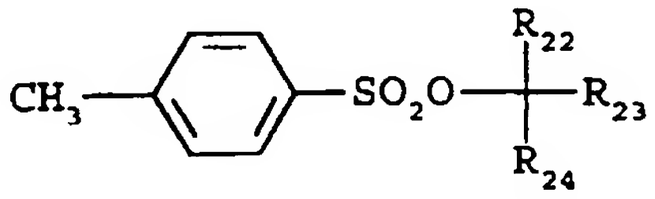
wherein $R_{22}$, $R_{23}$, and $R_{24}$ are defined as above, and Y is hydrogen or a group such that -O-Y is an activated leaving group.

In formula (III), Y is preferably: an alkylsulphonyl group (e.g. methanesulphonyl (mesyl)), optionally substituted by one or more fluorine atoms (e.g. trifluoromethanesulphonyl (trifyl) or 1,1,1-trifluoroethanesulphonyl); or an aryl-sulphonyl group (e.g. p-toluensulphonyl (tosyl), p-bromo-phenylsulphonyl (brosyl)).

Preferably it is:

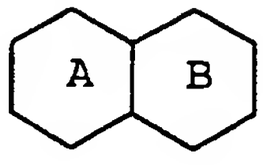



(IV) or




(V)

In formula (I) and (II) $R_{18}$ is preferably hydrogen or methyl,

while the moiety  may be selected, e.g., from:

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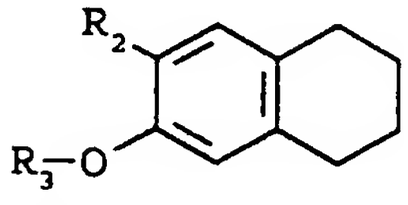
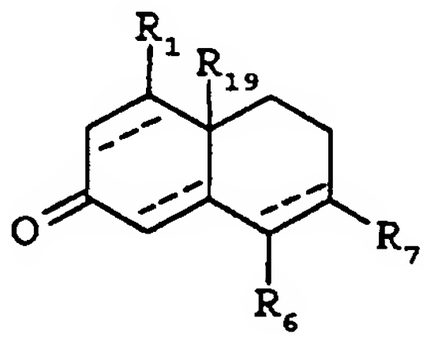


(VI)

wherein: $R_3$ is hydrogen or $C_1$-$C_4$ alkyl; and $R_2$ is hydrogen or $-OR_2'$, wherein $R_2'$ is hydrogen or $C_1$-$C_4$ alkyl;

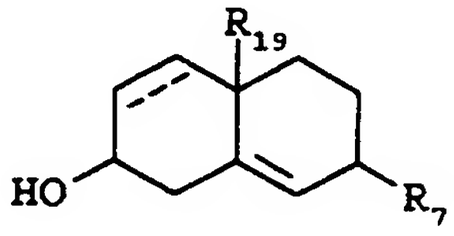
2)



(VII)

wherein: the symbols --- are, each independently, single or double bonds; $R_1$, $R_6$, $R_7$, and $R_{19}$ are, each independently, hydrogen or $C_1$-$C_4$ alkyl;

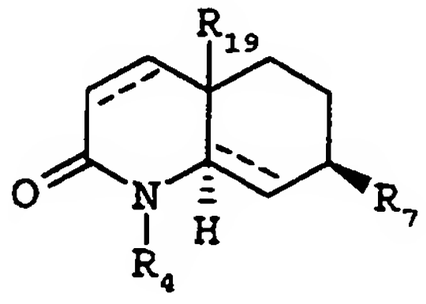
3)



(VIII)

wherein: the symbol --- is a single or a double bond; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl; and $R_{19}$ is hydrogen or $C_1$-$C_4$ alkyl;

4)

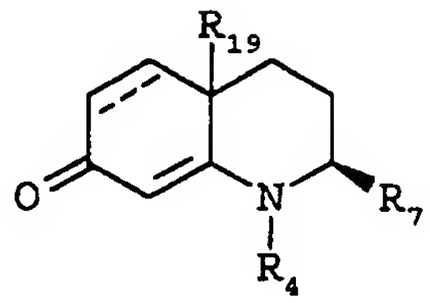


(IX)

wherein: the symbols --- are, each independently, single or double bonds; $R_4$ is hydrogen, $C_1$-$C_4$ alkyl, $C_6$-$C_{10}$ aryl, $C_7$-$C_{10}$ arylalkyl, acetyl, benzoyl, or tosyl; $R_7$ is hydrogen or $C_1$-$C_4$

alkyl; $R_{19}$ is hydrogen or $C_1$-$C_4$ alkyl;

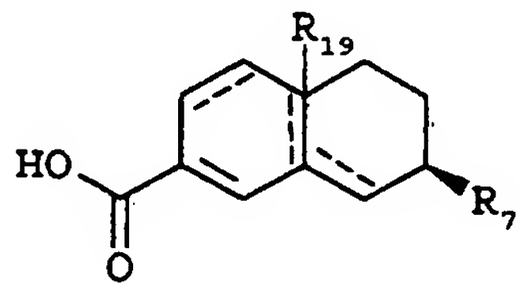
5)



(X)

wherein: the symbol --- is a single or a double bond; $R_4$ is hydrogen, $C_1$-$C_4$ alkyl, $C_6$-$C_{10}$ aryl, $C_7$-$C_{10}$ arylalkyl, acetyl, benzoyl, or tosyl; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl; $R_{19}$ is hydrogen or $C_1$-$C_4$ alkyl;

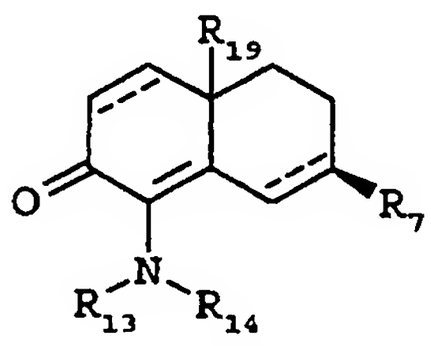
6)



(XI)

wherein: the symbols --- are, each independently, single or double bonds; $R_{19}$ is hydrogen, $C_1$-$C_4$ alkyl, or it is absent when linked to a double-bonded carbon atom; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl;

7)



(XII)

wherein: the symbols --- are, each independently, single or double bonds; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl; $C_{19}$ is hydrogen or $C_1$-$C_4$ alkyl; $R_{13}$ and $R_{14}$ are, each independently, hydrogen, $C_1$-$C_4$ alkyl, $C_6$-$C_{10}$ aryl, $C_7$-$C_{10}$ arylalkyl, acetyl, benzoyl, tosyl or, taken together, phthalyl.

A $C_1$-$C_5$ alkylene may be e.g.: $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$, $-CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH(CH_3)CH_2CH_2-$, or

$-CH(CH_3)CH_2CH_2CH_2-$.

A $C_1$-$C_4$ alkyl may have a straight or branched chain; for example it may be: methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, or tert-butyl.

A $C_1$-$C_{10}$ alkyl may have a straight or branched chain; for example, it may be: methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, sec-pentyl, neo-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, or n-decyl.

When substituted, a $C_1$-$C_{10}$ alkyl is preferably substituted by one or more halogen atoms, such as iodine, bromine, chlorine and/or fluorine. Chlorine and fluorine are preferred, fluorine is the most preferred. Particularly preferred substituted $C_1$-$C_{10}$ alkyl groups are those wherein all the hydrogen atoms are substituted by fluorine atoms, namely perfluoro groups such as, e.g.: $-CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, or $-CF(CF_3)_2$.

A $C_5$-$C_7$ cycloalkyl may be, e.g.: cyclopentyl, cyclohexyl or cycloheptyl.

A $C_6$-$C_{10}$ cycloalkylalkyl may be, for example, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cycloheptylmethyl, cycloheptylethyl, or cycloheptylpropyl.

An optionally substituted $C_6$-$C_{10}$ aryl is, e.g.: phenyl or naphthyl, optionally mono- or di-substituted by: halogen (preferably chlorine or fluorine), $C_1$-$C_4$ alkyl (preferably methyl, ethyl, n-propyl, n-butyl, iso-butyl), trifluoromethyl, cyano, methoxy, ethoxy, and/or nitro. Preferred optionally substituted $C_6$-$C_{10}$ aryls are, for example: phenyl, naphthyl, p-chlorophenyl, p-fluorophenyl, p-trifluorophenyl, p-cyanophenyl, p-methylphenyl, p-ethylphenyl, p-n-propylphenyl, p-n-butylphenyl, p-isobutylphenyl, p-methoxyphenyl,

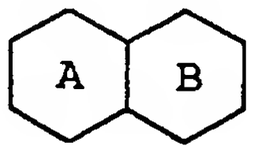
p-ethoxyphenyl, p-nitrophenyl, m-chlorophenyl, m-fluorophenyl, m-trifluorophenyl, m-cyanophenyl, m-methylphenyl, m-ethylphenyl, m-n-propylphenyl, m-n-butylphenyl, m-isobutylphenyl, m-methoxyphenyl, m-ethoxyphenyl, m-nitrophenyl, o-chlorophenyl, o-fluorophenyl, o-trifluorophenyl, o-cyanophenyl, o-methylphenyl, o-ethylphenyl, o-n-propylphenyl, o-n-butylphenyl, o-isobutylphenyl, o-methoxyphenyl, o-ethoxyphenyl, o-nitrophenyl, o,p-dimethylphenyl, o,p-difluorophenyl, o,p-dichlorophenyl, o,p-bistrifluoromethylphenyl, o,m-dimethylphenyl, o,m-difluorophenyl, o,m-dichlorophenyl, o,m-bistrifluoromethylphenyl, m,m-dimethylphenyl, m,m-dichlorophenyl, m,m-difluorophenyl, or m,m-bistrifluoromethylphenyl. Particularly preferred groups are: p-chlorophenyl, p-fluorophenyl, p-trifluorophenyl, p-cyanophenyl, p-methylphenyl, p-ethylphenyl, p-n-propylphenyl, p-n-butylphenyl, p-isobutylphenyl, p-methoxyphenyl, p-ethoxyphenyl, or p-nitrophenyl.

An optionally substituted $C_7$-$C_{14}$ arylalkyl may be, e.g.: benzyl or p-methoxybenzyl.

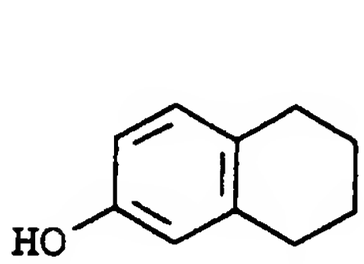
An optionally substituted $C_7$-$C_{14}$ alkylaryl group may be a $C_1$-$C_4$ alkyl substituted by one of the optionally substituted $C_6$-$C_{10}$ aryl groups as indicated hereinbefore, such as e.g.: p-chlorophenylmethyl, p-fluorophenylmethyl, p-trifluorophenylmethyl, p-methylphenylmethyl, p-ethylphenylmethyl, p-n-propylphenylmethyl, p-n-butylphenylmethyl, p-isobutylphenylmethyl, p-methoxyphenylmethyl, p-ethoxyphenylmethyl, p-nitrophenylmethyl, p-chlorophenylethyl, p-fluorophenylethyl, or p-trifluorophenylethyl. Among them, particularly preferred are: p-chlorophenylmethyl or p-fluorophenylmethyl.

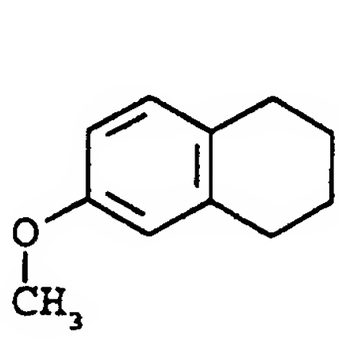
A heterocyclyl group may be, e.g., 4-piperidyl. A heteroaryl group may be, e.g., 4-pyridyl or 4,6-dimethyl-3-pyridyl. A heterocyclylalkyl group may be, e.g., N-piperidylmethyl, 2-N-

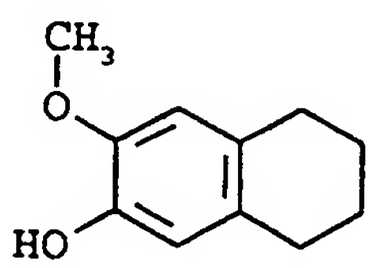
piperidylethyl, or N-morpholinomethyl. A heteroarylalkyl group may be, e.g., 4-pyridylmethyl.

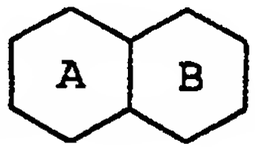
When the moiety 

has formula (VI), the $R_3$ group is preferably: hydrogen, methyl or ethyl, and the group $R_2$ is preferably: hydrogen, hydroxy, methoxy, or ethoxy. Particularly preferred moieties of formula (VI) are the following:

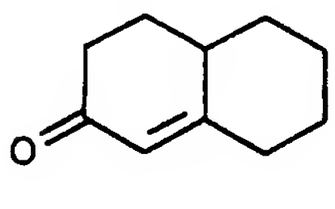


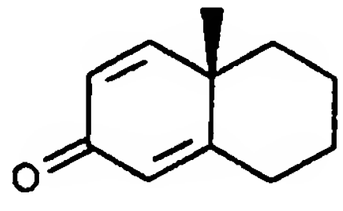


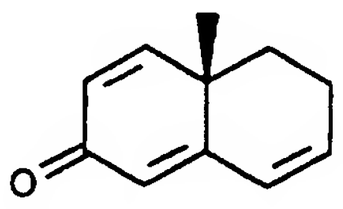


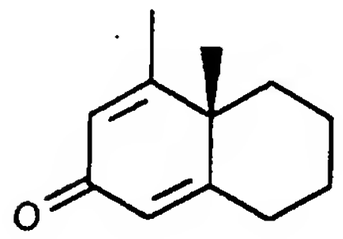

When the moiety 

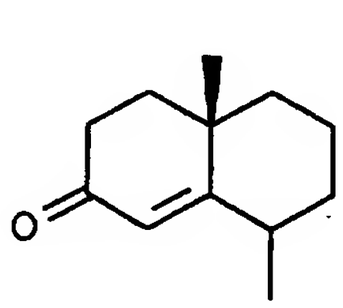
has formula (VII), the symbols --- may be single or double bonds, and the groups $R_1$, $R_6$, $R_7$ and $R_{19}$ are preferably, each independently, hydrogen or methyl. Particularly preferred moieties of formula (VII) are the following:

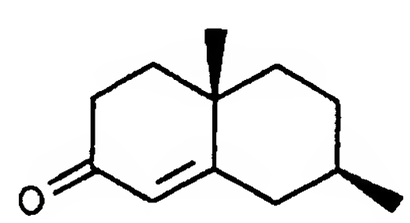


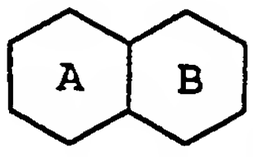






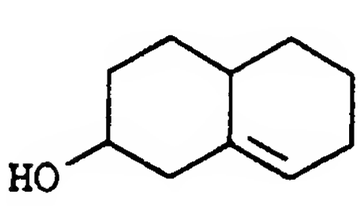


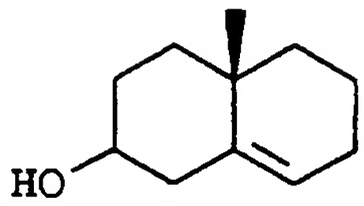


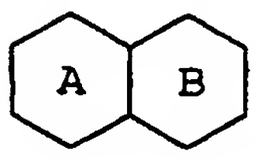

When the moiety 

has formula (VIII), the symbol --- may be a single or a double bond, and the groups $R_7$ and $R_{19}$ are preferably, each independently, hydrogen or methyl.

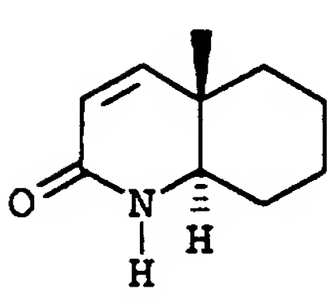
Particularly preferred moieties of formula (VIII) are the following:

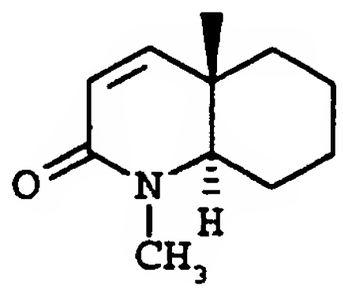


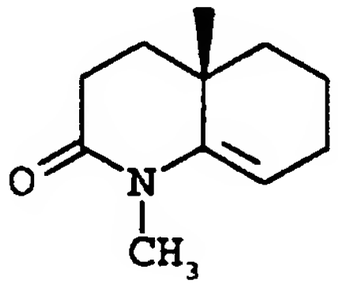


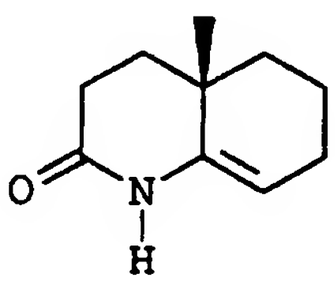
When the moiety  has formula (IX), the symbols --- may be, each independently, single or double bonds, the groups $R_7$ and $R_{19}$ are preferably, each independently, hydrogen or methyl, and the group $R_4$ is preferably: hydrogen, methyl, phenyl, benzyl, p-methoxyphenyl, acetyl, benzoyl, or tosyl.

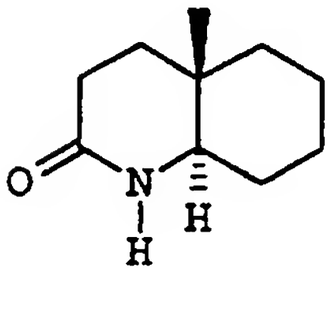
Particularly preferred moieties of formula (IX) are the following:

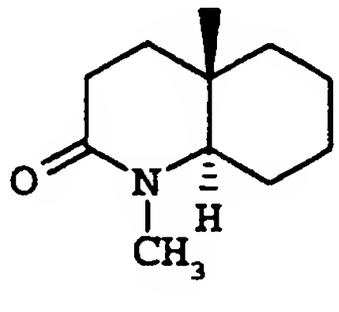


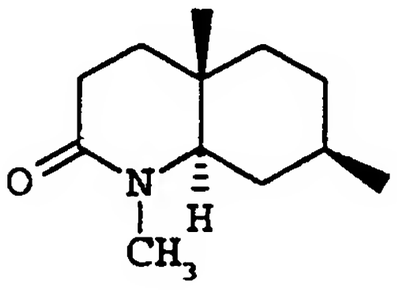


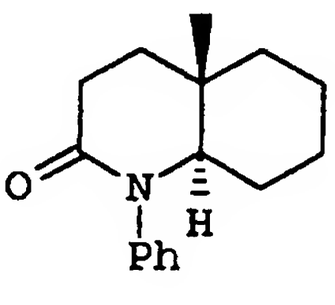


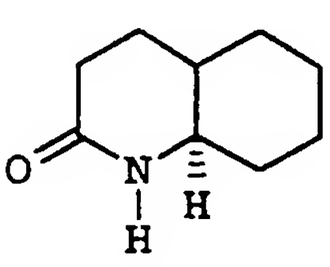


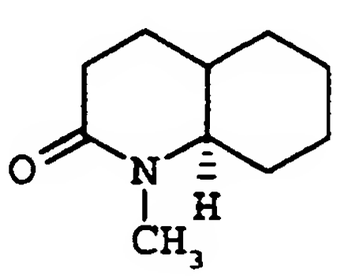


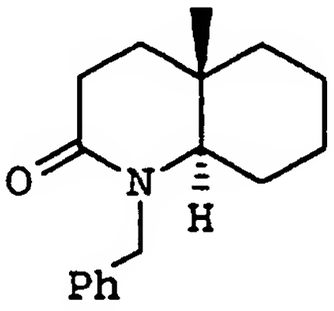


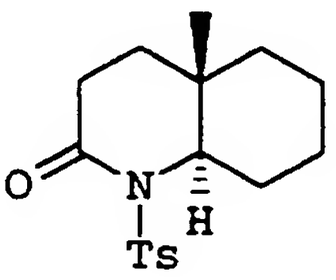


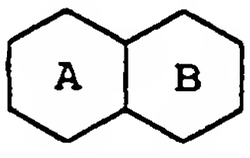




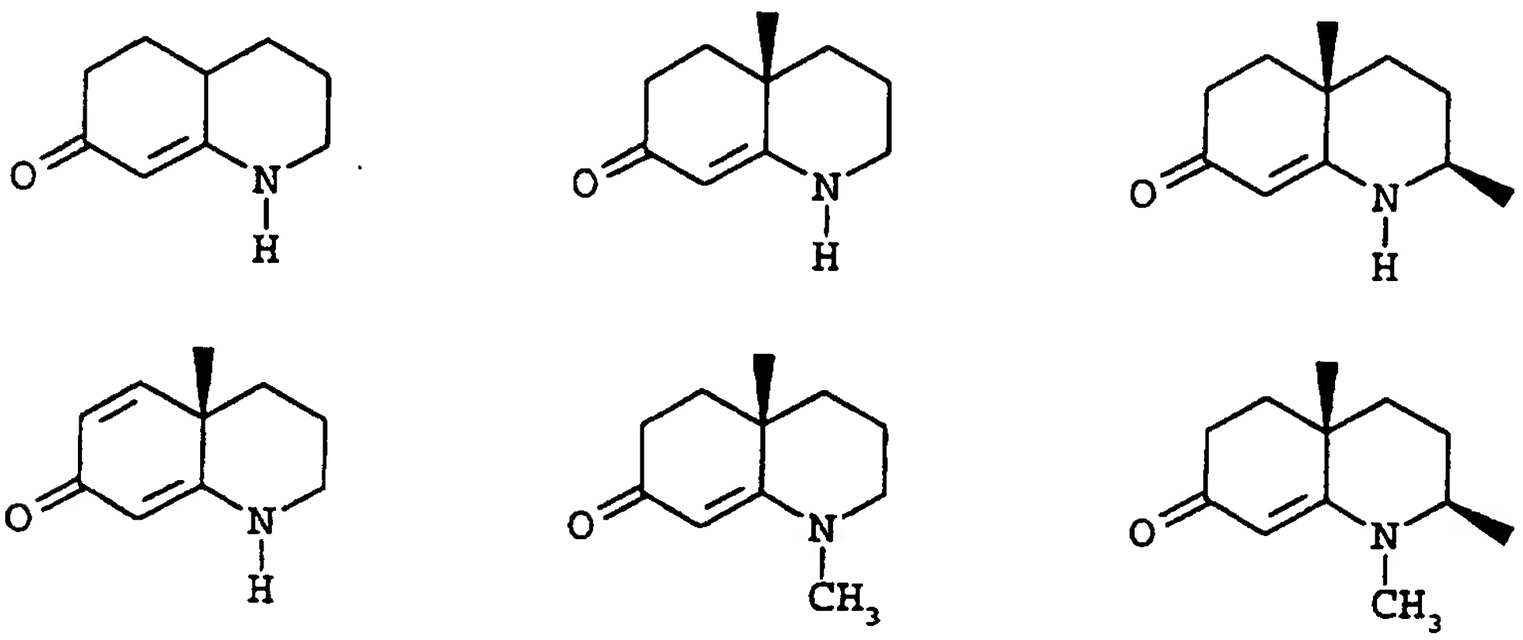


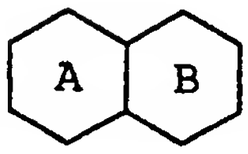




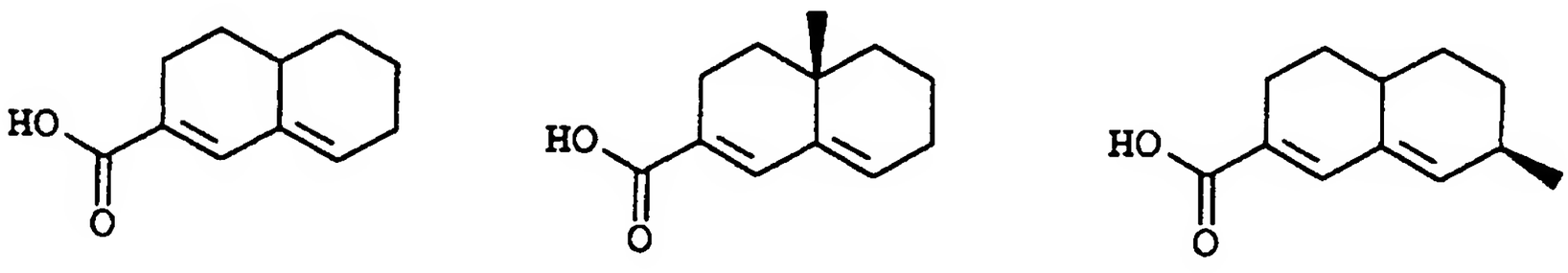
When the moiety  has formula (X), the symbol --- may be a single or a double bond, $R_7$ and $R_{19}$ are preferably, each independently, hydrogen or methyl, and $R_4$ is preferably: hydrogen, methyl, phenyl, benzyl, p-methoxyphenyl, acetyl,

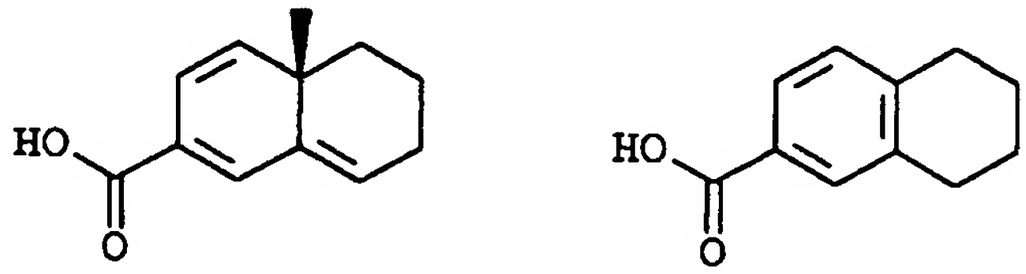
benzoyl, or tosyl. Particularly preferred moieties of formula (IX) are the following:

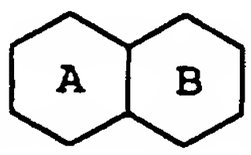


When the moiety 

has formula (XI), the symbols --- may be, each independently, single or double bonds, $R_7$ is preferably hydrogen or methyl, and $R_{19}$ is preferably hydrogen or methyl, or it is absent when linked to a double-bonded carbon atom. Particularly preferred moieties of formula (XI) are the following:

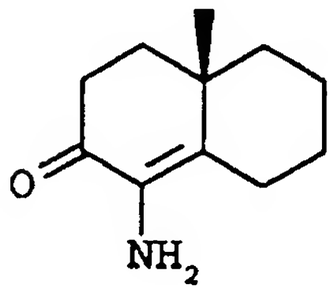
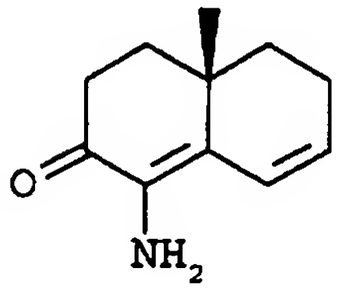
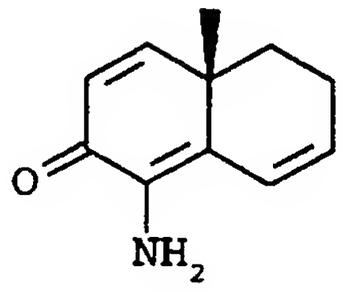
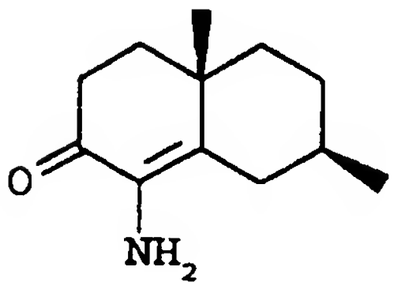
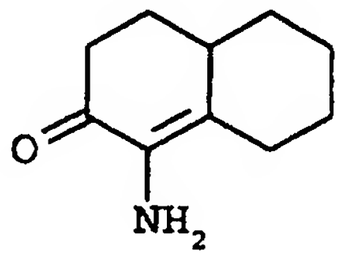




When the moiety 

has formula (XII), the symbols --- may be, each independently, single or double bonds, $R_7$ and $R_{19}$ are preferably, each independently, hydrogen or methyl; and $R_{13}$ and $R_{14}$ are preferably, each independently, hydrogen, methyl, phenyl, benzyl, acetyl, benzoyl, or tosyl, or, taken

together, phthalyl. Particularly preferred moieties of formula (XII) are the following:

The process of the present invention can be employed to prepare both 17α and 17β epimers, however 17β epimers are preferred.

The process object of the present invention can be advantageously carried out particularly to prepare steroids of formula (I) having at least one of $R_{22}$, $R_{23}$ and $R_{24}$ different from hydrogen, more particularly steroids of formula (I) having the carboxamide side-chain derivable from low reacting and/or sterically hindered amines. Therefore, the process of the present invention is preferably carried out to prepare steroids of formula (I) having a primary carboxamide side-chain (one of $R_{22}$, $R_{23}$ and $R_{24}$ different from hydrogen), more preferably a secondary carboxamide side-chain (two of $R_{22}$, $R_{23}$, and $R_{24}$ different from hydrogen), even more preferably a tertiary carboxamide side-chain ($R_{22}$, $R_{23}$, and $R_{24}$ different from hydrogen). Among the compounds of formula (I) having a tertiary carboxamide side-chain, those wherein one of $R_{22}$, $R_{23}$ and $R_{24}$ is an optionally substituted $C_6$-$C_{10}$ aryl group, and the other two are $C_1$-$C_4$ alkyl groups or $C_1$-$C_3$ perfluoroalkyl groups, are particularly preferred. Even more preferred are those compounds of formula (I) wherein one of the groups $R_{22}$, $R_{23}$, $R_{24}$ is an optionally substituted $C_6$-$C_{10}$

aryl group, and the other two are the same and are selected from $C_1$-$C_3$ perfluoroalkyl.

The process according to the present invention is preferably carried out to prepare one of the following steroids having a carboxamide side-chain:

1) N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

2) N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androstane-17β-carboxamide;

3) N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

4) N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide;

5) N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-16-ene-17β-carboxamide;

6) N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androst-16-ene-17β-carboxamide;

7) N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-oxo-androst-4-ene-17β-carboxamide;

8) N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3β-hydroxy-androst-5-ene-17β-carboxamide;

9) N-[1,1,1,3,3,3-hexafluoro-2-(p-methylphenyl)prop-2-yl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

10) N-[1,1,1,3,3,3-hexafluoro-2-(p-methylphenyl)prop-2-yl]-3-oxo-androst-4-ene-17β-carboxamide;

11) N-[1,1,1,3,3,3-hexafluoro-2-(p-fluorophenyl)prop-2-yl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

12) N-[1,1,1,3,3,3-hexafluoro-2-(p-fluorophenyl)prop-2-yl]-3-oxo-androst-4-ene-17β-carboxamide;

13) N-[1,1,1,3,3,3-hexafluoro-2-(p-chlorophenyl)prop-2-yl]-3-

oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

14) N-[1,1,1,3,3,3-hexafluoro-2-(p-chlorophenyl)prop-2-yl]-3-oxo-androst-4-ene-17β-carboxamide;

15) N-[1,1,1,3,3,3-hexafluoro-2-(p-trifluoromethyl)phenyl) prop-2-yl]3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

16) N-[1,1,1,3,3,3-hexafluoro-2-(p-trifluoromethylphenyl) prop-2-yl]3-oxo-androst-4-ene-17β-carboxamide;

17) N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

18) N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androstane-17β-carboxamide;

19) N-(1,1,1-trifluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

20) N-(1,1,1-trifluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide;

21) N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-16-ene-17β-carboxamide;

22) N-(1,1,1-trifluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androst-16-ene-17β-carboxamide;

23) N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-androst-4-ene-17β-carboxamide;

24) N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3β-hydroxy-androst-5-ene-17β-carboxamide;

25) N-(2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

26) N-(2-phenylprop-2-yl)-3-oxo-androst-4-ene-17β-carboxamide;

27) 17β-N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)carbamoyl-androsta-4,6-diene-3-carboxylate;

28) 17β-N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)carbamoyl-1,3,5(10)-estratriene-3-carboxylate;

29) N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)]-3-oxo-6-aza-androst-4-ene-17β-carboxamide; and

30) N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-hydroxyestra-1,3,5(10)-triene-17β-carboxamide.

In general, the reaction of a nitrile with an alcohol, an alkene, or an alkyl or aryl halide to yield the corresponding amide is known in organic chemistry as Ritter reaction or its modifications (see e.g. J. J. Ritter and P. P. Minieri, J. Am. Chem. Soc. 70, 4045 (1948); L. I. Krimen and D. J. Cota, Organic Reaction 17, 213-325 (1969); A. L. J. Beckwith in J. Zabicky, "The Chemistry of amides", Wiley, New York, 1970, pp. 125-130; J. Casanova in Z. Rappoport, "The chemistry of the cyano group", Wiley, New York, 1970, pp. 913-915; D. Dopp and H. Dopp in "Methoden der Organischen Chemie (Huben-Weil)", vol. E5, pp. 1032-1041; R. Bishop in B. Trost, "Comprehensive Organic Synthesis", Pergamon Press, 1991, vol. 6, pp. 261-300; Synthesis 274-276 (1979); Tetr. Lett. 30 (5), 581-582 (1989)).

The process according to the present invention may be generally carried out by treating a mixture of a nitrile of formula (II) and a compound of formula (III) or (IV) or (V), optionally in the presence of a solvent such as, for example, glacial acetic acid, acetic anhydride, di-n-butylether, chloroform, carbon tetrachloride, n-hexane, nitrobenzene, with a strong inorganic acid such as, for example, perchloric acid, phosphoric acid, 98% sulfuric acid, fluorosulfonic acid, or with a strong organic acid, such as, for example, trifluoromethanesulfonic acid, trifluoroacetic acid, at a

temperature ranging from about room temperature to about the reflux temperature of the reaction mixture, for a time varying from about 30 minutes to about 8 hours, preferably in inert atmosphere of, for example, nitrogen or argon.

Preferably, the process of the present invention is carried out using a compound of formula (III), wherein Y is a trifluoromethanesulfonyl group. In this case the process is generally carried out by adding to the mixture of the nitrile of formula (II) and the triflate of formula (III), as pure liquids or dissolved in a solvent, an organic acid such as, for example, trifluoroacetic acid or trifluoroethanol or trifluoromethanesulfonic acid or glacial acetic acid, and then stirring the mixture at a temperature ranging from about room temperature to the reflux temperature of the reaction mixture, preferably from 50° to 70°C, for a time varying from about 30 minutes to about 8 hours, in inert atmosphere of, for example, nitrogen. The reaction mixture is worked up by treatment with an aqueous alkaline solution (for example, a saturated sodium bicarbonate solution) and extracted with an organic solvent.

The starting compounds of formula (II), (III), (IV) and (V) are known compounds and/or can be obtained by methods well known to anyone skilled in the art. Particularly, the compounds of formula (II) wherein the AB ring moiety has formula (VI) are disclosed e.g. in EP-A-677134; the compounds of formula (II) wherein the AB ring moiety has formula (VII) may be obtained from the corresponding 17-carboxylic acids described e.g. in U.S. Patents No. 4,191,759, 4,220,775 and 4,377,584; the compounds of formula (II) wherein the AB ring moiety has formula (VIII) are described e.g. in: Collection Czechoslov. 18, 407, 410, 412 (1953); Berichte 71, 1487-1492

(1938); the compounds of formula (II) wherein the AB ring moiety has formula (IX) are described e.g. in: EP-A-4949, EP-A-277002, J. Med. Chem. 27, 1690-1701 (1984) and 29, 2298-2351 (1986); the compounds of formula (II), wherein the AB ring moiety has formula (X) may be obtained from the corresponding 17-carboxylic acids described e.g in WO 93/13124 and J.Med.Chem. 37, 2352-2360 (1994); the compounds of formula (II) wherein the AB ring moiety has formula (XI) are described e.g. in EP-A-289327; the compounds of formula (II) wherein the AB ring moiety has formula (XII) may be obtained from the corresponding 17-carboxylic acids described e.g in EP-469,548 and EP-469,548.

The 17-cyanosteroids of formula (II) can be advantageously obtained by dehydration of the corresponding 17-carboxamides, according to the method reported in Synthesis 591-592 (1982). This synthetic route is especially advantageous for those compounds, such as the azasteroids, that cannot be subjected to severe dehydration conditions, such as chlorinating dehydratating agents in refluxing high-boiling solvents (e.g. thionyl chloride in dimethylformamide).

The following working examples are given to better illustrate the present invention, and cannot be construed as a limitation to the scope of the invention itself.

**EXAMPLE 1**

**N-(1,1,1,3,3,3-hexafluoro-2-phenyl-2-propyl)-3-oxoandrost-4-ene-17β-carboxamide**

[compound (I), wherein the moiety AB has formula (VII), wherein $R_1$=H, $R_6$=H, $R_7$=H and $R_{19}$=Me, the $C_4$-$C_5$ bond is a double bond, $R_{18}$=Me, Z=single bond, $R_{22}$=$R_{24}$=$CF_3$, $R_{23}$=Ph].

To a stirred mixture of 17β-cyanoandrost-4-en-3-one (100 mg, 0.335 mmol) and 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propyl trifluoromethanesulfonate (252 mg, 0.669 mmol), under nitrogen atmosphere, trifluoroacetic acid (0.13 ml, 1.806 mmol) was added at room temperature. The mixture was then stirred at 60°C for 3 hrs. The reaction mixture was cooled in an ice bath, a saturated aqueous solution of sodium hydrogen carbonate (5 ml) was added, and the mixture was extracted with diethylether (3 x 10 ml). The combined organic extracts were washed with water until neutral, dried on sodium sulfate and the solvent was removed under vacuum. The crude product was purified by flash chromatography (eluant: n-hexane/ethyl acetate 70:30) to yield 72 mg (40%) of the title compound.

NMR ($CDCl_3$) δ: 0.77 (s, 3H, Me (18)), 1.29 (s, 3H, Me (19)), 5.72 (m, 1H, CH (4)), 5.93 (s, 1H, NH), 7.36-7.55 (m, 5H, Ph).

Following an analogous procedure, starting from the corresponding 17β-cyanosteroids and the suitable triflate, the compounds listed below were prepared:

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3β-hydroxy-androst-5-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-methylphenyl)prop-2-yl]-3-oxo-androst-4-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-fluorophenyl)prop-2-yl]-3-oxo-androst-4-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-chlorophenyl)prop-2-yl]-3-oxo-androst-4-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-trifluoromethylphenyl)prop-2-yl]-3-oxo-androst-4-ene-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-androst-4-ene-

17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3β-hydroxy-androst-5-ene-17β-carboxamide; and

N-(2-phenylprop-2-yl)-3-oxo-androst-4-ene-17β-carboxamide.

**EXAMPLE 2**

**N-(1,1,1,3,3,3-hexafluoro-2-phenyl-2-propyl)-4-methyl-3-oxo-4-aza-5α-androst-16-ene-17β-carboxamide**

[compound (I), wherein the moiety AB has formula (IX), wherein $R_4$=Me, $R_7$=H, and $R_{19}$= Me, the $C_{16}$-$C_{17}$ bond is a double bond, $R_{18}$= Me, A = single bond, $R_{22}$=$R_{24}$=$CF_3$, $R_{23}$=Ph].

To a stirred mixture of 17β-cyano-4-methyl-4-aza-5α-androst-16-en-3-one (100 mg, 0.321 mmol) and 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propyl trifluoromethanesulfonate (241 mg, 0.642 mmol), under nitrogen atmosphere, trifluoroacetic acid (129 mg, 1.605 mmol) was added at room temperature. The mixture was heated to 80°C for 5 hrs. After cooling in an ice bath, water (5 ml) and then a saturated aqueous solution of sodium hydrogen carbonate (5 ml) were added and the mixture was extracted with methylene chloride (2 x 5 ml). The combined organic extracts were washed with water until neutral, dried with sodium sulfate, and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography (eluant: toluene/ethyl acetate/methanol 75:20:5) to yield 76 mg (42%) of the title compound.

NMR ($CDCl_3$) δ: 0.93 (s, 3H, Me (19)), 1.00 (s, 3H, Me (18)), 2.93 (s, 3H, N-Me), 3.07 (dd, 1H, H (5α)), 6.17 (s, 1H, NH ), 6.54 (m, 1H, H (16)), 7.77-7.55 (m, 5H, Ph).

MS ($FAB^+$): 557 $(M + H)^+$

Following an analogous procedure, starting from the corresponding 17β-cyano-16-unsaturated-steroids and the suitable triflate, the compounds listed below were obtained:

N-(1,1,1,3,3,3-Hexafluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-16-ene-17β-carboxamide;

N-(1,1,1,3,3,3-Hexafluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androst-16-ene-17β-carboxamide;

N-(1,1,1-Trifluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androst-16-ene-17β-carboxamide; and

N-(1,1,1-Trifluoro-2-phenylprop-2-yl)-3-oxo-androst-4-ene-17β-carboxamide.

**EXAMPLE 3**

**(a) 3-Oxo-4-aza-5α-androst-1-ene-17β-carboxamide**

A solution of thionyl chloride (25 ml) in anhydrous chloroform (10 ml) was added dropwise, under nitrogen atmosphere, to a suspension of 3-oxo-4-aza-5α-androst-1-ene-17β-carboxylic acid (5.0 g) in anhydrous chloroform (250 ml), over about 30 minutes, at 0°C. After stirring at room temperature for 1 h, the volatile products were removed under reduced pressure and the white solid of 3-oxo-4-aza-5α-androst-1-ene-17β-carbonyl chloride so obtained was dissolved in anhydrous chloroform (800 ml), cooled to 0°C and treated with gaseous anhydrous ammonia for 30 minutes. After stirring the solution for 1 h at room temperature, the solvent was removed under vacuum, the residue treated with 1N sodium carbonate aqueous solution (100 ml) and extracted with methylene chloride (3 x 100 ml). The combined organic extracts were dried with sodium sulfate and the solvent

evaporated under reduced pressure. 5.0 g of the crude title compound were obtained.

NMR ($CDCl_3$) δ: 0.73 (s, 3H, Me (18)), 0.96 (s, 3H, Me (19)), 3.33 (dd, 1H, H (5α)), 5.25 (bs, 1H, NH (4)), 5.37 (bs, 2H, $CONH_2$) 5.81 (dd, 1H, H (2)), 6.80 (d, 1H, H (1)).

NMR (DMSO) δ: 0.59 (s, 3H, Me (18)), 0.84 (s, 3H, Me (19)), 3.18 (dd, 1H, H(5α)), 5.62 (dd, 1H, H(2)), 6.75 and 6.95 (d, 2H, $CONH_2$), 6.84 (d, 1H, H(1)), 7.43 (m, 1H, NH).

IR (nujol) $cm^{-1}$: 3430, 3185, 1690, 1675, 1655, 1610.

**(b) 17β-cyano-4-aza-5α-androst-1-en-3-one**

[compound (II) wherein the moiety AB has formula (IX), wherein $R_4$=H, $R_7$=H, $R_{19}$=Me and the $C_1$-$C_2$ is a double bond, $R_{18}$=Me, A=single bond].

3-Oxo-4-aza-5α-androst-1-ene-17β-carboxamide (1.00 g) was added to a solution of trimethylsilylpolyphosphate (2.94 g) in chloroform (35 ml) and the mixture was refluxed for 4 hrs. After cooling, a 25% aqueous solution of sodium carbonate (100 ml) was added, the organic layer was separated and the aqueous phase was extracted with methylene chloride (3 x 100 ml). The combined organic extracts were washed with water until neutral, dried with sodium sulfate and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography on silica gel (eluant: methylene chloride/acetone 70:30) to yield 580 mg of the title compound.

NMR ($CDCl_3$) δ: 0.93 (s, 3H, Me (18)), 0.98 (s, 3H, Me (19)), 3.33 (dd, 1H, H (5α)), 5.66 (bs, 1H, NH (4)),

5.81 (dd, 1H, H (2)), 6.80 (d, 1H, H (1)).

IR (nujol) $cm^{-1}$: 3400, 2240, 1670, 1597.

**(c) N-[1,1,1,3,3,3-Hexafluoro-2-phenylprop-2-yl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide**

[compound (I) wherein the moiety AB has formula (IX), wherein $R_4$=H, $R_7$=H, $R_{19}$=Me and the $C_1$-$C_2$ is a double bond, $R_{18}$=Me, A= single bond, $R_{22}$=$R_{24}$=$CF_3$, $R_{23}$=Ph].

To a stirred mixture of 17β-cyano-4-aza-5α-androst-1-en-3-one (2.5 g) and 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propyl trifluoromethanesulfonate (6.4 g), trifluoroacetic acid (3.139 ml) was added at room temperature, under nitrogen atmosphere. The reaction mixture was heated at 60°C for 3 hrs. After cooling to about 0°C, the reaction mixture is diluted with diethylether (10 ml), additioned with a saturated sodium bicarbonate aqueous solution (20 ml), and then extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were washed with water until neutral, dried with sodium sulfate, and the solvent was evaporated at reduced pressure. The crude solid so obtained was purified by flash chromatography on silica gel (eluant: toluene/ethyl acetate/methanol 75:20:5) to yield 1.90 g (42%) of the title compound.

NMR ($CDCl_3$) δ: 0.76 (s, 3H, Me(18)), 0.98 (s, 3H, Me(19)), 3.33 (dd, 1H, H(5α)), 5.39 (s, 1H, NH(4)), 5.82 (dd, 2H, H(2)), 5.89 (s, 1H, NH(21)), 6.79 (d, 1H, H(1)), 7.38-7.54 (m, 5H, Ph).

MS ($FAB^-$) (m/z): 542 $[M-H]^-$, 471 $[M-CHF_3-H]^-$.

IR (nujol) $cm^{-1}$: 3440, 3260, 3210, 1705, 1670, 1597.

Following an analogous procedure, starting from the

corresponding 17β-cyano-4-aza-5α-androstanes and the suitable triflate, the compounds listed below were prepared:

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androstane-17β-carboxamide;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-methylphenyl)prop-2-yl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-fluorophenyl)prop-2-yl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-chlorophenyl)prop-2-yl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-trifluoromethyl)phenyl)prop-2-yl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androstane-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide; and

N-(2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide.

Analogously, starting from the corresponding 17β-

cyanosteroids and triflates, the following compounds may be obtained:

17β-N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)carbamoyl-androsta-4,6-diene-3-carboxylate;

17β-N-(2-methyl-2-propyl)carbamoyl-androsta-4,6-diene-3-carboxylate;

17β-N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)carbamoyl-1,3,5(10)-estratriene-3-carboxylate;

17β-N-(2-methyl-2-propyl)carbamoyl-1,3,5(10)-estratriene-3-carboxylate;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-4-amino-3-oxoandrost-4-ene-17β-carboxamide;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-4-amino-3-oxoandrosta-4,6-diene-17β-carboxamide;

N-(2-methyl-2-propyl)-4-amino-3-oxoandrost-4-ene-17β-carboxamide;

N-(2-methyl-2-propyl)-4-amino-3-oxoandrosta-4,6-diene-17β-carboxamide;

N-(diphenylmethyl)-3-oxo-6-aza-androst-4-ene-17β-carboxamide;

N-[bis-(p-fluorophenyl)methyl]-3-oxo-6-aza-androst-4-ene-17β-carboxamide;

N-[bis-(p-chlorophenyl)methyl]-3-oxo-6-aza-androst-4-ene-17β-carboxamide;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-oxo-6-aza-androst-4-ene-17β-carboxamide; and

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-hydroxyestra-1,3,5(10)-triene-17β-carboxamide.

**EXAMPLE 4**

**N-[1,1,1,3,3,3-Hexafluoro-2-phenylprop-2-yl]-3-oxo-4-azaandrost-5-ene-17β-carboxamide**

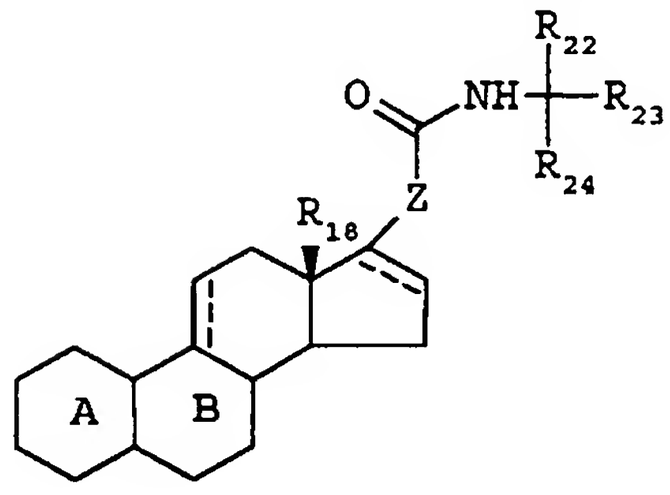
[compound (I) wherein the moiety AB has formula (IX), wherein $R_4$=H, $R_7$=H, $R_{19}$=Me and the $C_1$-$C_2$ is a single bond, $C_5$-$C_6$ is a double bond, $H_5$ is not present, $R_{18}$=Me, A=single bond, $R_{22}$=$R_{24}$=$CF_3$, $R_{23}$=Ph].

To a stirred mixture of 17β-cyano-4-azaandrost-5-en-3-one (2.98 g) and 1,1,1,3,3,3-hexafluoro-2-phenyl-2-propyl trifluoromethanesulfonate (7.23 g) trifluoroacetic acid (3.7 mL) is added at room temperature, under nitrogen atmosphere. The reaction mixture is heated to 60°C for 5 h. After cooling to about 0°C, the reaction mixture is diluted with methylene chloride (15 mL), a 35% NaOH solution (5mL) is added dropwise at 4°C followed by water (21 mL) and extracted with methylene chloride (2 x 15 mL). The combined organic extracts are washed with water until neutral, dried over sodium sulfate and the solvent is evaporated at reduced pressure. The crude solid so obtained is purified by flash chromatography on silica gel (eluant: ethyl acetate/n-hexane/methanol 75:20:5) to yield 912 mg of the title compound.

NMR ($CDCl_3$) δ : 0.76 (s, 3H, Me(18)), 1.13 (s, 3H, Me(19)), 2.34 (t, 1H, H(17α)), 2.46-2.52 (m, 2H, $CH_2$(2)), 4.82 (m, 1H, H(6)), 5.82 (s, 1H, NH(21)), 7.38 (s,1H,NH(4)), 7.35-7.55 (m, 5H, Ph).

## CLAIMS

1. Process for preparing a compound of formula:

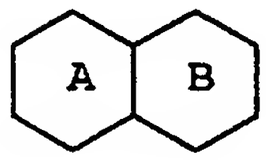


(I)

wherein:

the symbols --- are, each independently, single or double bonds;

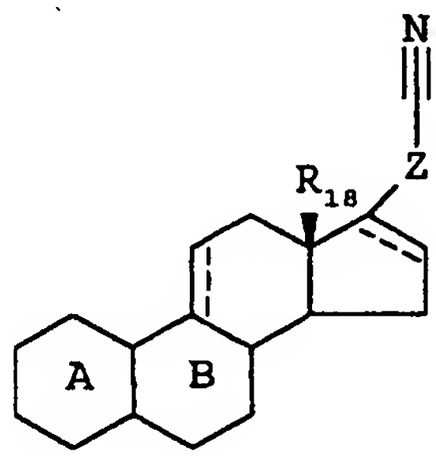
Z is a single bond, or a straight or branched $C_1$-$C_5$ alkylene;

the moiety  represents the A and B rings of a steroid;

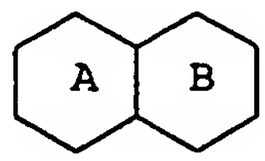
$R_{18}$ is hydrogen or $C_1$-$C_4$ alkyl;

$R_{22}$, $R_{23}$, and $R_{24}$ are, each independently, selected from: hydrogen; optionally substituted $C_1$-$C_{10}$ alkyl, $C_5$-$C_7$ cycloalkyl, $C_6$-$C_{10}$ alkylcycloalkyl or cycloalkylalkyl, $C_6$-$C_{10}$ aryl, $C_7$-$C_{14}$ arylalkyl or alkylaryl, heterocyclyl, heteroaryl, heterocyclylalkyl, and heteroarylalkyl;

said process comprising reacting a compound of formula:

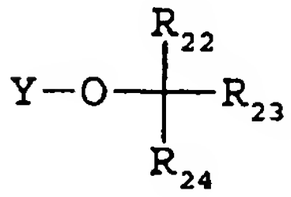


(II)

wherein the symbols --- , Z, $R_{18}$, and the moiety 

are defined as above;

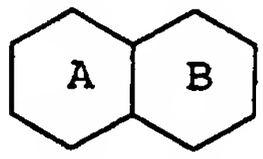
with a compound of formula:



(III)

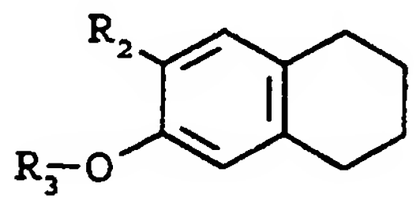
wherein $R_{22}$, $R_{23}$, and $R_{24}$ are defined as above, and Y is hydrogen or a group such that -O-Y is an activated leaving group.

2. The process according to claim 1, wherein the moiety



is selected from:

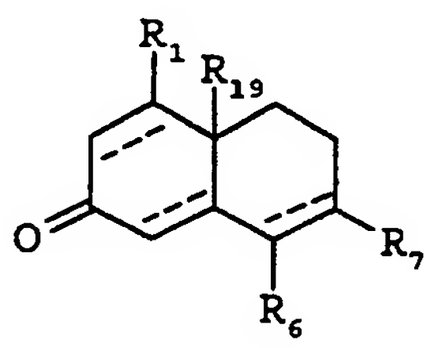
1)



(VI)

wherein: $R_3$ is hydrogen or $C_1$-$C_4$ alkyl; and $R_2$ is hydrogen or $-OR_2'$, wherein $R_2'$ is hydrogen or $C_1$-$C_4$ alkyl;

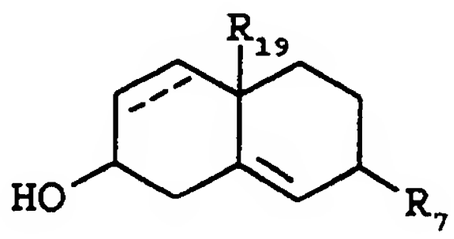
2)



(VII)

wherein: the symbols --- are, each independently, single or double bonds; $R_1$, $R_6$, $R_7$, and $R_{19}$ are, each independently, hydrogen or $C_1$-$C_4$ alkyl;

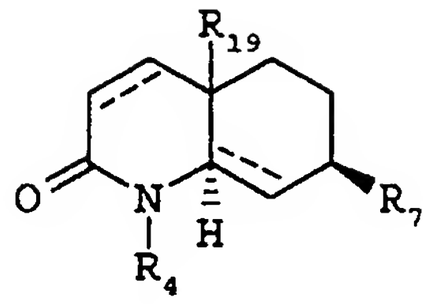
3)



(VIII)

wherein: the symbol --- is a single or a double bond; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl; and $R_{19}$ is hydrogen or $C_1$-$C_4$ alkyl;

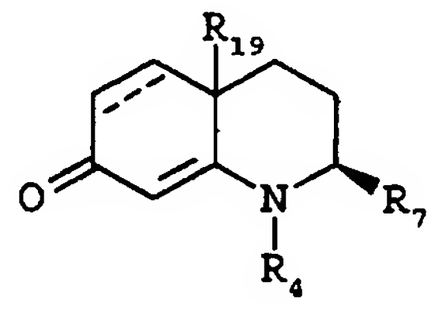
4)



(IX)

wherein: the symbols --- are, each independently, single or double bonds; $R_4$ is hydrogen, $C_1$-$C_4$ alkyl, $C_6$-$C_{10}$ aryl, $C_7$-$C_{10}$ arylalkyl, acetyl, benzoyl, or tosyl; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl; $R_{19}$ is hydrogen or $C_1$-$C_4$ alkyl;

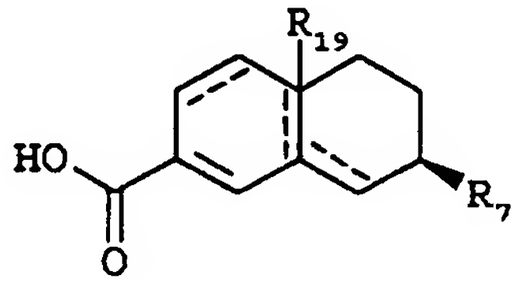
5)



(X)

wherein: the symbol --- is a single or a double bond; $R_4$ is hydrogen, $C_1$-$C_4$ alkyl, $C_6$-$C_{10}$ aryl, $C_7$-$C_{10}$ arylalkyl, acetyl, benzoyl, or tosyl; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl; $R_{19}$ is hydrogen or $C_1$-$C_4$ alkyl;

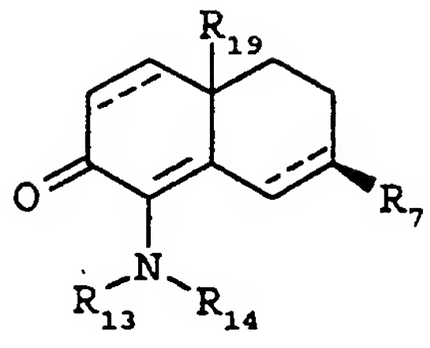
6)



(XI)

wherein: the symbols --- are, each independently, single or double bonds; $R_{19}$ is hydrogen, $C_1$-$C_4$ alkyl, or it is absent when linked to a double-bonded carbon atom; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl;

7)



(XII)

wherein: the symbols --- are, each independently, single or double bonds; $R_7$ is hydrogen or $C_1$-$C_4$ alkyl; $C_{19}$ is hydrogen or $C_1$-$C_4$ alkyl; $R_{13}$ and $R_{14}$ are, each independently, hydrogen, $C_1$-$C_4$ alkyl, $C_6$-$C_{10}$ aryl, $C_7$-$C_{10}$ arylalkyl, acetyl, benzoyl, tosyl or, taken together, phthalyl.

3. The process according to claim 1, wherein one of $R_{22}$, $R_{23}$ and $R_{24}$ is an optionally substituted $C_6$-$C_{10}$ aryl group, and the other two are $C_1$-$C_4$ alkyl groups or $C_1$-$C_3$ perfluoroalkyl groups.

4. The process according to claim 1, wherein the compound of formula (I) is selected from:

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androstane-17β-carboxamide;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-16-ene-17β-carboxamide;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androst-16-ene-17β-carboxamide;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-oxo-androst-4-

ene-17β-carboxamide;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3β-hydroxy-androst-5-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-methylphenyl)prop-2-yl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-methylphenyl)prop-2-yl]-3-oxo-androst-4-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-fluorophenyl)prop-2-yl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-fluorophenyl)prop-2-yl]-3-oxo-androst-4-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-chlorophenyl)prop-2-yl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-chlorophenyl)prop-2-yl]-3-oxo-androst-4-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-trifluoromethyl)phenyl) prop-2-yl]3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-[1,1,1,3,3,3-hexafluoro-2-(p-trifluoromethylphenyl) prop-2-yl]3-oxo-androst-4-ene-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androstane-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-4-meth l-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-16-ene-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-4-methyl-3-oxo-4-aza-

5α-androst-16-ene-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3-oxo-androst-4-ene-17β-carboxamide;

N-(1,1,1-trifluoro-2-phenylprop-2-yl)-3β-hydroxy-androst-5-ene-17β-carboxamide;

N-(2-phenylprop-2-yl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide;

N-(2-phenylprop-2-yl)-3-oxo-androst-4-ene-17β-carboxamide;

17β-N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)carbamoyl-androsta-4,6-diene-3-carboxylate;

17β-N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)carbamoyl-1,3,5(10)-estratriene-3-carboxylate;

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)]-3-oxo-6-aza-androst-4-ene-17β-carboxamide; and

N-(1,1,1,3,3,3-hexafluoro-2-phenylprop-2-yl)-3-hydroxyestra-1,3,5(10)-triene-17β-carboxamide.

5. The process according to claim 1, wherein in formula (III) Y is selected from: alkylsulphonyl groups, optionally substituted by one or more fluorine atoms; and aryl-sulphonyl groups.

# INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/EP 97/01626

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07J73/00 C07J41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 93 14107 A (SMITHKLINE BEECHAM CORP) 22 July 1993<br>see example 7E<br>--- | 1-5 |
| X | US 4 348 327 A (NICKOLSON ROBERT ET AL) 7 September 1982<br>see the whole document<br>----- | 1-5 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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1

| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 26 June 1997 | 16.07.97 |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax ( + 31-70) 340-3016 | Authorized officer<br>Watchorn, P |

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